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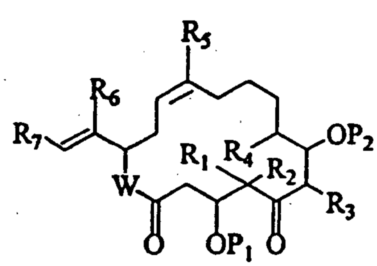
(54) Title: A PROCESS FOR THE REDUCTION OF OXIRANYL EPOTHILONES TO OLEFINIC EPOTHILONES



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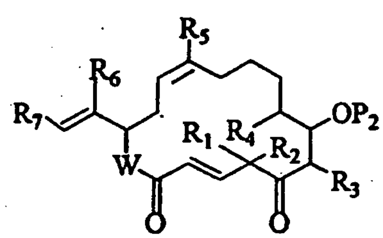


(IV)

(57) Abstract: The invention as claimed is directed to a process for making an epothilone having structures (II) or (IV) from ones having an oxiranyl moiety, by reacting a compound having the latter structure with a metal or metal-assisted reagent. Said metal or metal-assisted reagent is selected from the group consisting of a) reactive metallocenes; b) [$N_2C(CO_2Me)_2$, cat Rh_2,$(OAC)_4$]; c) [$N_2C(CO_2Me)_2$, cat[(n-$C_7H_{15}CO_2)_2$ Rh]$_2$]; d) [Zn-Cu, EtOH]; e) [Mg(Hg), MgBr]; f) Cr; g) [$FeCl_3$, n-BuLi]; h) [$TiCl_3$, $LiAlH_4$]; i) [$TiCl_4$, Zn]; j) [WCl_6, $LiAlH_4$]; k) [$NbCl_5$, $NaAlH_4$]; l) [VCl_3,Zn] and m) [WCl_6, n-BuLi].

WO 00/71521 A1

A PROCESS FOR THE REDUCTION OF OXIRANYL EPOTHILONES TO OLEFINIC EPOTHILONES

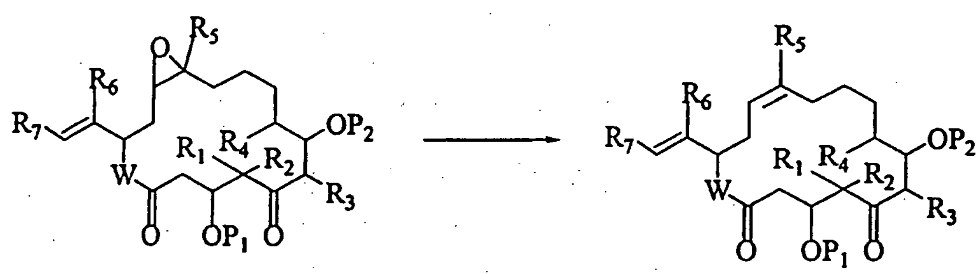
This is a continuation-in-part of Application Serial No. 09/170,581, filed October 13, 1998, which claims the benefit of U. S. Provisional Application Serial Nos. 60/082,563, filed April 21, 1998, and 60/067,549, filed December 4, 1997; said U. S. patent applications are hereby incorporated by reference as if set forth at length.

Field of the Invention

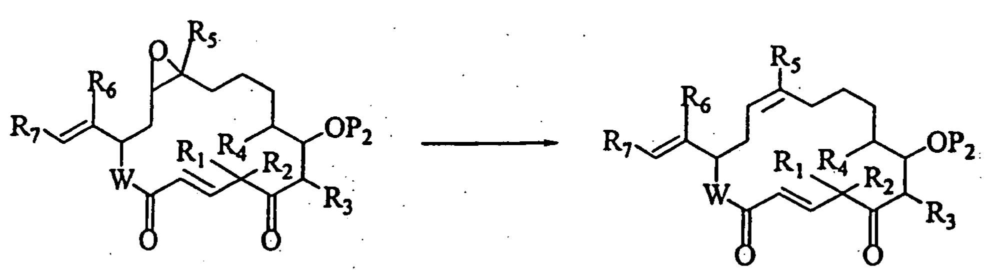
The present invention relates to a process for the preparation of olefinic epothilones from oxiranyl epothilones.

Brief Description of the Invention

The present invention is directed to a process for preparing compounds of formulas II and IV.



I II



III IV

The compounds of formulas I - IV are useful in the treatment of a variety of cancers and other abnormal proliferative diseases. Compounds of formula I are disclosed in Hofle *et al.*, *Angew. Chem. Int. Ed. Engl.*, 1996, 35, No 13/14, 1567; WO93/10121 published May 27, 1993, and WO97/19086 published May 29, 1997, and also Nicolaou *et al.*, *Angew Chem. Int. Ed. Engl.*, 1997, 36, No. 19, 2097 and Su *et al.*, *Angew Chem. Int. Ed. Engl.*, 1997, 36, No. 19, 2093. Compounds of formula III are disclosed in Hofle *et al.*, WO 97/19086 published May 29, 1997. As used in formulas II and IV, and throughout the specification, the symbols have the following meanings:

W is O or NR_8;

R_1, R_2, R_3, R_4, R_5, R_6, are selected from the group H, alkyl, substituted alkyl, or aryl and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl;

R_7 is selected from the group consisting of H, alkyl, substituted alkyl, aryl, cycloalkyl, or heterocyclo;

R_8 is H, alkyl, or substituted alkyl, OH, O-alkyl, O-substituted alkyl;

P_1 and P_2 are selected from the group, H, alkyl, substituted alkyl, alkanoyl, substituted alkanoyl, aroyl, substituted aroyl, trialkylsilyl, aryl dialkylsilyl, diaryl alkylsilyl, triarylsilyl.

Detailed Description of the Invention

Definitions:

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group substituted by, for example, one to four substituents, such as, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, cycloalkyoxy, heterocylooxy, oxo, alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, cycloalkylamino, heterocycloamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or

aralkyl, alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido (e.g. SO_2NH_2), substituted sulfonamido, nitro, cyano, carboxy, carbamyl (e.g. $CONH_2$), substituted carbamyl (e.g. CONH alkyl, CONH aryl, CONH aralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl), alkoxycarbonyl, aryl, substituted aryl, guanidino and heterocyclos, such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Where noted above where the substituent is further substituted it will be with halogen, alkyl, alkoxy, aryl or aralkyl.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, biphenyl and diphenyl groups, each of which may be substituted.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "substituted aryl" refers to an aryl group substituted by, for example, one to four substituents such as alkyl; substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, cycloalkyloxy, heterocyclooxy, alkanoyl, alkanoyloxy, amino, alkylamino, aralkylamino, cycloalkylamino, heterocycloamino, dialkylamino, alkanoylamino, thiol, alkylthio, cycloalkylthio, heterocyclothio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, alkysulfonyl, sulfonamido, aryloxy and the like. The substituent may be further substituted by halo, hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

The term "cycloalkyl" refers to a optionally substituted, saturated cyclic hydrocarbon ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and adamantyl. Exemplary

substituents include one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

The terms "heterocycle", "heterocyclic" and "heterocyclo" refer to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl sulfone, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1, 1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic heterocyclic groups include benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl,

quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

Exemplary substituents include one or more alkyl groups as described above or one or more groups described above as alkyl substituents. Also included are smaller heterocyclos, such as, epoxides and aziridines.

The term "alkanoyl" refers to -C(O)-alkyl.

The term "substituted alkanoyl" refers to -C(O)-substituted alkyl.

The term "aroyl" refers to -C(O)-aryl.

The term "substituted aroyl" refers to -C(O)-substituted aryl.

The term "trialkylsilyl" refers to -Si(alkyl)$_3$.

The term "aryl dialkylsilyl" refers to -Si(alkyl)$_2$(aryl).

The term "diaryl alkylsilyl" refers to -Si(aryl)$_2$(alkyl).

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

The term "metallocene" refers to an organometallic coordination compounds obtained as a cyclopentadienyl derivative of a transition metal or metal halide. For examples, *see*, Hawley's Condensed Chemical Dictionary, Twelfth Edition, Van Nostrand Reinhold Company, New York, 1993.

The term "metal-assisted reagent" refers to a reagent that is activated in the presence of a metal. For example, diazodimethyl malonate is activated in the presence of a rhodium catalyst, to give the corresponding reactive carbene.

Use and Utility:

The compounds of the invention are microtubule-stabilizing agents. They are thus useful in the treatment of a variety of cancers, including (but not limited to) the following;

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma;
- hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burketts lymphoma;

- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
- other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma;
- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;
- tumors of mesenchymal origin, including fibrosarcoma, rhabdomyoscaroma, and osteosarcoma; and
- other tumors, including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.

Compounds of the invention may also inhibit tumor angiogenesis, thereby affecting the growth of tumors. Such anti-angiogenesis properties of the compounds of formulas II and IV may also be useful in the treatment of certain forms of blindness related to retinal vascularization, arthritis, especially inflammatory arthritis, multiple sclerosis, restinosis and psoriasis.

Compounds of the invention may induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds of formula II and IV, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including cancer (particularly, but not limited to follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostrate and ovary, and precancerous lesions such as familial adenomatous polyposis), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), autoimmune diseases (including, but not limited to, systemic lupus erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, and autoimmune diabetes mellitus), neurodegenerative disorders (including, but not limited to, Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), AIDS, myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol induced liver

diseases, hematological diseases (including, but not limited to, chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including, but not limited to, osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases, and cancer pain.

The compounds of this invention are also useful in combination with known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. Compounds of formulas II and IV can be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate. Especially useful are cytotoxic drug combinations wherein the second drug chosen acts in a different phase of the cell cycle, e.g. S phase, than the present compounds of formulas II and IV which exert their effects at the G_2-M phase.

The compounds of the invention may exist as multiple optical, geometric and stereoisomers. While the process and schemes herein are depicted for one optical orientation, included within the present invention are all isomers and mixtures thereof.

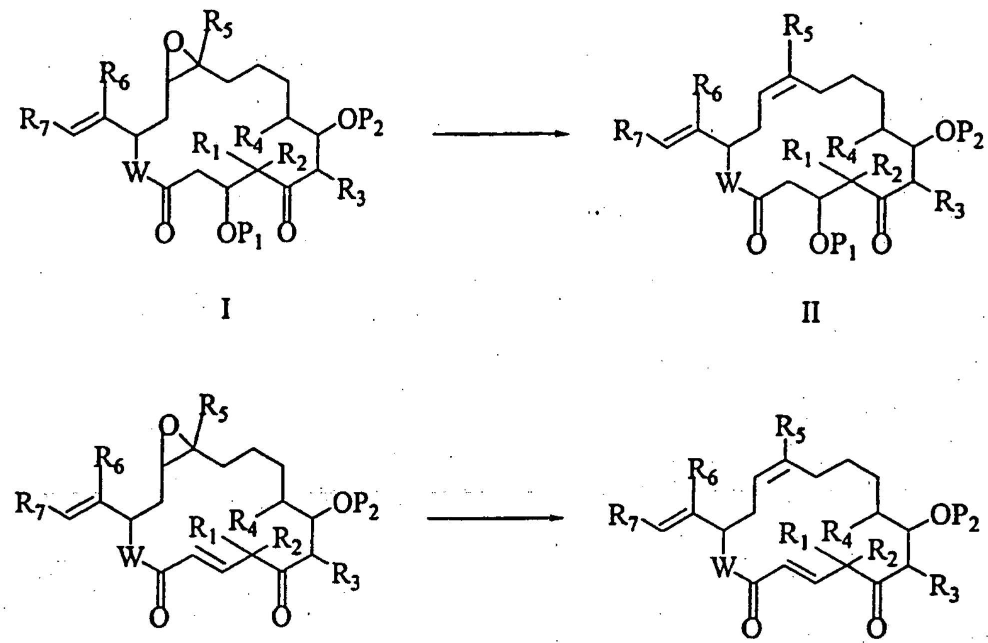
The compounds of this invention can be formulated with a pharmaceutical vehicle or diluent for oral, intravenous or subcutaneous administration. The pharmaceutical composition can be formulated in a classical manner using solid or liquid vehicles, diluents and additives appropriate to the desired mode of administration. Orally, the compounds can be administered in the form of tablets, capsules, granules, powders and the like. The compounds are administered in a dosage range of about 0.05 to 200 mg/kg/day, preferably less than 100 mg/kg/day, in a single dose or in 2 to 4 divided doses.

Methods of Preparation:

Compounds of the invention can be prepared from compounds and by the methods described in the following schemes.

Compounds of formulas II and IV are prepared from compounds of formulas I and III, as shown in Scheme 1.

Scheme 1



I II

III IV

A compound of formula I or III affords compounds of formula II or, respectively, when treated with a reactive metallocene such as titanocene, zirconocene or niobocene (*see*, for example, R. Schobert and U. Hohlein, *Synlett*, 1990, No. 8, 465-466.). Optionally, compounds of formulas II or IV where P_1 and/or P_2 are hydroxyl protecting groups such as silanes, *e.g.*, trialkylsilyl, and the like, can be deprotected by methods known in the art to provide compounds of formula II or IV where P_1 and P_2 are hydrogen. Other hydroxyl-protecting groups which are known in the art, and defined above as P_1 and P_2, can also be used (*see*, T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, Inc., New York, 1991).

Alternatively, other metal or metal-assisted reagents as listed below can be used for the conversion of a compound of formula I or III to a compound of formula II or IV. The protocols of these representative examples are incorporated herein as if set forth at length.

1) $N_2C(CO_2Me)_2$, cat $Rh_2(OAc)_4$:

Martin, M.G., Ganem, B., *Tett. Lett.*, 1984, *25*, 251.

2) $N_2C(CO_2Me)_2$, cat $[(n\text{-}C_7H_{15}CO_2)_2Rh]_2$:

Rancher, S., Ki-Whan, C., Ki-Jun, H., Burks, J., *J. Org. Chem.*, 1986, *51*, 5503.

3) Zn-Cu, EtOH:

Kupchen, S.M, Maruyama, M., *J. Org. Chem.*, 1971, *36*, 1187.

4) Mg(Hg), $MgBr_2$:

Bertini, F., Grasselli, P., Zubiani, G., Cainelli, G., *Chem. Commun.*, 1970, 144.

5) Cr:

Gladysz, J.A., Fulcher, J.G., Togashi, S. *J., Org. Chem.*, 1976, *41*, 3647.

6) $FeCl_3$, *n*-BuLi:

Fujisawa, T., Sugimoto, K., Ohta, H., *Chem. Lett,*. 1974, 883.

7) $TiCl_3$, $LiAlH_4$:

McMurry, J.E, Fleming, M.P., *J. Org. Chem.*, 1975, *40*, 2555.

McMurry, J.E., Silvestri, M.G., Fleming, M.P., Hoz, T., Grayston, M.W., *J. Org. Chem.*, 1978, *43*, 3249.

8) $TiCl_4$, Zn:

McMurry, J.E., Silvestri, M.G., Fleming, M.P., Hoz, T., Grayston, M.W., *J. Org. Chem.*, 1978, *43*, 3249.

9) WCl_6, $LiAlH_4$:

Fugiwara, Y., Ishikawa, R., Akiyama, F., Teranishi, S., *J. Org. Chem.*, 1978, *43*, 2477.

10) $NbCl_5$, $NaAlH_4$:

Sato, M, Oshima, K., *Chem. Lett.*, 1982, 157.

11) VCl_3, Zn:

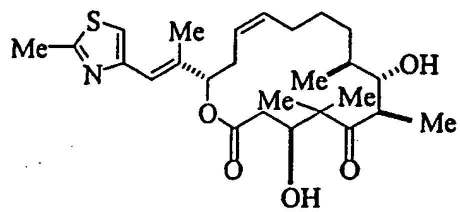
Inokuchi, T., Kawafuchi, H., Torii, S., *Synlett*, 1992, *6*, 510.

12) WCl_6, *n*-BuLi:

Sharpless, K.B., Umbret, M.A., Nieh, M.T., Flood, T.C., *J. Am. Chem. Soc.*, 1972, *94*, 6538.

Preparation of the compounds of the present invention is illustrated in more detail by reference to the following non-limiting examples.

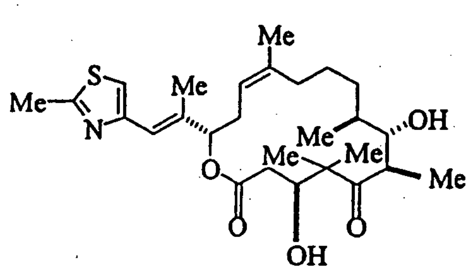
Example 1



[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13(Z)-cyclohexadecene-2,6-dione. [Epothilone C]

To a two-necked flask was added chopped pieces of magnesium turnings (24 mg, 1.0 mmol). The flask was flame-dried under vacuum and cooled under argon. Bis(cyclopentadienyl)titanium dichloride (250 mg, 1.0 mmol) was added followed by anhydrous THF (5 mL). The stirring suspension was evacuated with low vacuum, and the reaction flask was refilled with argon. The red suspension became dark, turning a homogeneous deep green after 1.5 hours with nearly all the magnesium metal being consumed. An aliquot (3.5 mL, 0.70 mmol, 3.5 equivalents) was removed and cooled to -78 °C under argon. To this solution was added epothilone A (99 mg, 0.20 mmol, 1.0 equivalent). The reaction mixture was warmed to room temperature and stirred for 15 minutes. The volatiles were removed *in vacuo* and the residue was chromatographed two times on silica (25g), eluting with 35% EtOAc/hexanes to give 76 mg (80%) of the title compound as a pale yellow viscous oil.

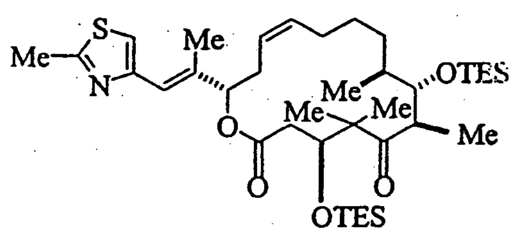
Example 2



[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13(Z)-cyclohexadecene-2,6-dione. [Epothilone D]

To anhydrous THF (5 ml) at -78°C under argon was added WCl_6 (198 mg, 0.5 mmol) followed by *n*BuLi (0.625 ml of 1.6 *M* solution in hexanes, 1.0 mmol). The reaction was allowed to warm to room temperature over a 20 minute period. An aliquot (0.50 ml, 0.05 mmol) of the tungsten reagent was removed and added to epothilone B (9.0 mg, 0.018 mmol) under argon and the reaction mixture was stirred for 15 minutes, and then quenched by the addition of saturated $NaHCO_3$ (1 ml). The reaction mixture was extracted with EtOAc (3 x 1 ml), the combined extracts dried (Na_2SO_4), filtered, and the volatiles were removed under vacuum. The residue was chromatographed with 35% EtOAc/hexanes to give the title compound (7.0 mg, 0.014 mmol). MS *m/z*: 492.3 (M^++H).

Example 3



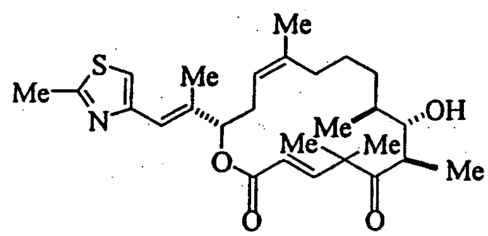
[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Triethylsilyloxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13(Z)-cyclohexadecene-2,6-dione. [Bis-Triethylsilyl Epothilone C]

Et_3SiCl (4.15 mmol, 0.700 ml) was added to epothilone A (0.415 mmol, 205 mg), imidazole (2.07 mmol, 140 mg) and *i*-Pr_2EtN (6.22 mmol, 1.08 ml) in DMF (5 ml). The resulting solution was heated at 40 °C. After 16 hours, additional Et_3SiCl (2.07 mmol, 0.350 ml) and *i*-Pr_2EtN (4.15 mmol, 0.725 ml) were added and the resulting solution stirred at 60°C for 48 hours. The reaction was concentrated, and the residue was purified with flash chromatography (10% EtoAc/Hexanes). Bis-

triethylsilyl epothilone A was isolated as colorless oil (264 mg, 88%). MS (M^++H) 722.

To anhydrous THF (5 ml) at -78°C under argon was added WCl_6 (198 mg, 0.5 mmol) followed by nBuLi (0.625 ml of 1.6 *M* solution in hexanes, 1.0 mmol). The reaction was allowed to warm to room temperature over a 20 minute period. An aliquot (1.0 ml, 0.089 mmol) of the tungsten reagent was removed and added to bis-triethylsilyl epothilone A (22.5 mg, 0.031 mmol) under argon and the reaction stirred for 20 minutes then quenched by the addition of saturated $NaHCO_3$ (1 ml). The reaction mixture was extracted with EtOAc (3 x 1 ml), the combined extracts dried (Na_2SO_4), filtered, and the volatiles were removed under vacuum. The residue was chromatographed with 10% EtOAc/hexanes to give the title compound (13.6 mg, 0.019 mmol) in 62% yield. MS *m/z*: 706.5 (M^++H).

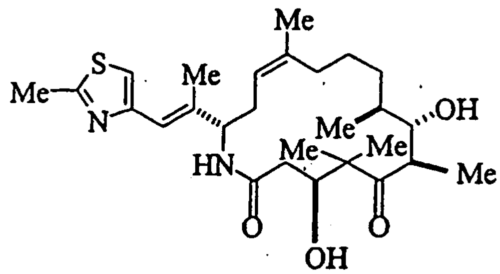
Example 4



[7R-[7R*,8S*,9S*,15R*(E)]]-8-Hydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxa-3(E),13(Z)-cyclohexadecadiene-2,6-dione.

The title compound was prepared following the procedure described in Example 2. From 10 mg of [1S-[1R*,3R*(E),10S*,11S*,12R*,16S*]]-11-hydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadec-6-ene-5,9-dione (prepared from epothilone B using the procedure described in WO97/19086 for the analogous conversion of epothilone A), 4.5 mg of title compound was obtained. MS 474 $(M+H)^+$.

Example 5



[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione

A. (3S,6R,7S,8S,12R,13S,15S)-15-Azido-12,13-epoxy-4,4,6,8,12,16-hexamethyl-7-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-16-heptadecenoic acid.

A solution of epothilone B (0.35 g, 0.69 mmol) in degassed THF (4.5 mL) was treated with a catalytic amount (80 mg, 69 mmol) of tetrakis(triphenylphosphine) palladium (0) and the suspension was stirred at 25°C, under argon for 30 minutes. The resulting bright yellow, homogeneous solution was treated all at once with a solution of sodium azide (54 mg, 0.83 mmol) in degassed H_2O (2.2 mL). The reaction mixture was warmed to 45°C for 1 h, diluted with H_2O (5 mL) and extracted with EtOAc (4 x 7 mL). The organic extracts were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 3.0 x 15 cm, 95:5.0:0.5 $CHCl_3$-MeOH-AcOH) to afford Compound A (0.23 g, 61%) as a colorless oil. MS (ESI^+): 551 $(M+H)^+$; MS(ESI^-): 549 $(M-H)^-$.

B. (3S,6R,7S,8S,12R,13S,15S)-15-Amino-12,13-epoxy-4,4,6,8,12,16-hexamethyl-7-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-16-heptadecenoic acid.

A solution of Compound A (0.23 g, 0.42 mmol) in THF (4.0 mL) was treated with H_2O (23 mL, 1.25 mmol) and polymer supported triphenylphosphine (Aldrich, polystyrene cross-linked with 2% DVB, 0.28 g, 0.84 mmol) at 25°C. The resulting suspension was stirred at 25°C under argon (32 hours), filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2,

1.5 x 10 cm, 95:5.0:0.5 to 90:10:1.0 $CHCl_3$-MeOH-AcOH gradient elution) to afford Compound B (96 mg, 44%) as a colorless oil. MS (ESI^+): 525.2 $(M+H)^+$; MS (ESI^-): 523.4 $(M-H)^-$.

Alternatively, to a 25 mL round-bottom flask charged with Compound A (0.26 g, 0.47 mmol) and PtO_2 (0.13 g, 50 wt %) was added absolute EtOH under argon. The resulting black mixture was stirred under one atmosphere of H_2 for 10 hours, after which time the system was purged with N_2 and an additional portion of PtO_2 (65 mg, 25 wt %) was added. Once again the reaction mixture was stirred under a blanket of H_2 for 10 hours. The system was then purged with N_2, and the reaction mixture was filtered through a Celite pad eluting with CH_2Cl_2 (3 x 25 mL). The solvents were removed *in vacuo* and the residue was purified as described above to afford Compound B (0.19 g, 75%).

Alternatively, a solution of Compound A (20 mg, 36 mmol) in THF (0.4 mL) was treated with triphenylphosphine (19 mg, 73 mmol) under argon. The reaction mixture was warmed to 45°C, stirred for 14 hours and cooled to 25°C. The resulting iminophosphorane was treated with ammonium hydroxide (28%, 0.1 mL) and once again the reaction mixture was warmed to 45°C. After 4 hours, the volatiles were removed *in vacuo* and the residue was purified as described above to afford Compound B (13 mg, 70%).

C. [1S-[1R*,3R*(E),7R*,10S*,11S*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione.

A solution of Compound B (0.33 g, 0.63 mmol) in degassed DMF (250 mL) was treated with solid $NaHCO_3$ (0.42 g, 5.0 mmol) and diphenylposphoryl azide (0.54 mL, 2.5 mmol) at 0°C under argon. The resulting suspension was stirred at 4°C for 24 hours, diluted with phosphate buffer (250 mL, pH=7) at 0°C and extracted with EtOAc (5 x 100 mL). The organic extracts were washed with 10% aqueous LiCl (2 x 125 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was first purified by flash chromatography (SiO_2, 2.0 x 10 cm, 2-5 % MeOH-$CHCl_3$ gradient elution) and then repurified using a Chromatotron (2 mm SiO_2, GF rotor, 2-5% MeOH-$CHCl_3$ gradient elution) to afford the title compound (0.13 g, 40%) as a colorless oil: ^1H

NMR ($CDCl_3$, 400 MHz) d 6.98 (s, 1 H), 6.71 (d, 1H, NH, J = 8.1 Hz), 6.56 (s, 1 H), 4.69-4.62 (m, 1 H), 4.18-4.12 (m, 1 H), 4.01-3.96 (m, 1 H), 3.86 (s, 1 H), 3.38-3.34 (m, 1 H), 2.82 (dd, 1 H, J = 5.6, 6.0 Hz), 2.71 (s, 3 H), 2.58 (s, 1 H), 2.43 (dd, 1 H, J = 9.0, 14.5 Hz), 3.34 (dd, 1 H, J = 3.0, 14.5 Hz), 2.14 (s, 3 H), 2.05-1.92 (m, 2 H), 1.82-1.41 (a series of multiplets, 7 H), 1.35 (s, 3 H), 1.28 (s, 3 H), 1.18 (d, 3 H, J = 6.8 Hz), 1.14 (s, 3 H), 1.00 (d, 3 H, J = 6.8 Hz); MS (ESI$^+$): 507.2 $(M+H)^+$;

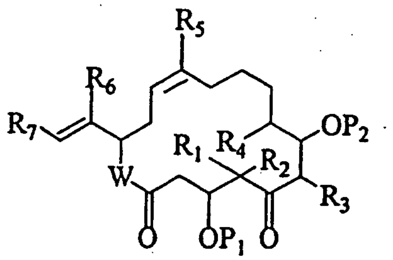
MS(ESI$^-$): 505.4 $(M-H)^-$.

D. [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione

Tungsten hexachloride (0.19 g, 0.49 mmol, 0.5 equivalents) was dissolved in THF (5.0 ml) and the solution was cooled to -78°C. n-Butyllithium in hexane (1.6M, 0.63 ml, 1.0 mmol, 1.0 equiv) was added in one portion and the reaction mixture was allowed to warm to room temperature over 20 minutes (the solution turned dark green upon warming to room temperature). A 0.1M solution of the prepared tungsten reagent (0.79 ml, 0.079 mmol, 2.0 mmol) was added to Compound C (0.020 g, 0.039 mmol, 1.0 equivalent) at room temperature. The reaction mixture was stirred at room temperature for 30 minutes and then was quenched with saturated $NaHCO_3$ (2.0 ml). The quenched solution was diluted with water (10 ml) and the solution was extracted with CH_2Cl_2 (4X20 ml). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum. The inorganics were removed by passing the residue through a silica gel plug (eluting with 19/1 $CHCl_3$/MeOH). The eluent was concentrated under vacuum. The residue was purified by phplc (YMC-S5 ODS, 30-100% B, A=5% aqueous CH_3CN, B=95% aqueous CH_3CN, 3 ml/min, 220 nm, 30 minutes gradient) and the appropriate fractions were concentrated under vacuum. The sticky solid was lyophilized from aqueous acetonitrile to afford title compound (4.3 mg, 29%) as a white solid. TLC: Rf = 0.57 (9/1 $CHCl_3$/MeOH, visualization by UV), HRMS: (M+H)+ calc = 491.29436, found = 491.2934

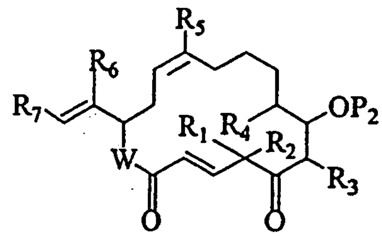
What is claimed:

1. A process to produce a compound of the formulas



II

or



IV

wherein

W is O or NR_8;

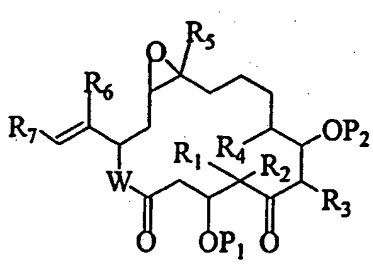
R_1, R_2, R_3, R_4, R_5, R_6, are selected from the group H, alkyl, substituted alkyl, or aryl and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl;

R_7 is selected from the group consisting of H, alkyl, substituted alkyl, aryl, cycloalkyl, or heterocyclo;

R_8 is H, alkyl, or substituted alkyl, OH, O-alkyl, O-substituted alkyl; and

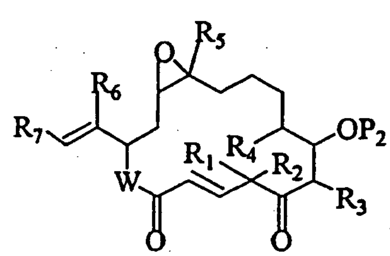
P_1 and P_2 are selected from the group, H, alkyl, substituted alkyl, alkanoyl, substituted alkanoyl, aroyl, substituted aroyl, trialkylsilyl, aryl dialkylsilyl, diaryl alkylsilyl, triarylsilyl;

which comprises reacting a compound of the formula



I

or



III

wherein

W, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, P_1 and P_2 are defined as above;

with a metal or metal-assisted reagent, wherein said metal or metal-assisted reagent are selected from the group consisting of a) reactive metallocenes; b) [$N_2C(CO_2Me)_2$, cat Rh_2,$(OAC)_4$]; c) [$N_2C(CO_2Me)_2$, cat[(n-$C_7H_{15}CO_2)_2$ Rh]$_2$]; d) [Zn-Cu, EtOH]; e) [Mg(Hg), MgBr]; f) Cr; g) [$FeCl_3$, n-BuLi]; h) [$TiCl_3$, $LiAlH_4$]; i) [$TiCl_4$, Zn]; j) [WCl_6, $LiAlH_4$,]; k) [$NbCl_5$, $NaAlH_4$]; l) [VCl_3,Zn] and m) [WCl_6, n-BuLi].

2. The process of claim 1 wherein the metal or metal-assisted reagent is a metallocene.

3. The process of claim 2 wherein the metallocene is selected from the group consisting of titanocene, zirconocene or niobocene.

4. The process of claim 1 wherein the metal or metal-assisted reagent is [WCl_6, n-BuLi].

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/13253

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 225/02, 225/04, 313/06, 313/16
US CL : 540/461, 463; 549/270, 271

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 540/461, 463; 549/270, 271

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/19086 (HOELFE et al.) 29 May 1997 (28.05.1997), pages 1-4.	1-5
Y	SCHOBERT et al., Reduction and Isomerization of Oxiranes and alfa-Diazoketones by Various Early Transition Metallocenes. Synlett (1990), No. 8, pages 465-466	1-5
Y	SHARPLESS et al., Lower Valent Tungsten Halides. A New Class of Reagents for Deoxygenation of Organic Molecules. Journal of the American Chemical Society, 94(18), 06 September 1972, pages 6538-6540.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2000 (19.06.2000)	04 AUG 2000

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